Attorney's Docket No. US-109

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	
HIRANO et al.	Art Unit: 1652
Application No.: 10/784,986	Examiner: Gebreyesus, Kagnew H.
Filing Date: February 25, 2004	Attorney Ref. No.: US-109
For: NOVEL LYSINE DECARBOXYLASE GENE AND METHOD FOR PRODUCING L-LYSINE	Confirmation No.: 1388

BRIEF FOR APPELLANT

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

COMES NOW the Appellant to present this Brief in support of the appeal of the final rejections of Claims 8, 9, 12, and 13 in the above-captioned patent application. The Notice of Appeal, Petition for 1-Month Extension of Time, and Pre-Appeal Brief Request for Review were filed on June 14, 2006. As the 1-month time period for response from the mailing of the Notice of Panel Decision from Pre-Appeal Brief Review, mailed on October 30, 2006, is greater than the two-month time period running from the filing of the Notice of Appeal of June 14, 2006 (which has expired), this Brief is due to be filed on November 30, 2006. Therefore, this brief is timely filed.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. If, however, additional extensions of time are necessary to prevent abandonment of this application or dismissal of this appeal, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is hereby authorized to charge fees necessitated by this paper, and to credit all refunds and overpayments, to the credit account utilized in EFS-Web processing.

For the following reasons, Appellant respectfully submits that the rejection of each of Claims 8, 9, 12, and 13 in this application is in error, and therefore respectfully requests reversal of the rejections.

TABLE OF CONTENTS

I. Real Party in Interest

The real party in interest is Ajinomoto Co., Inc, a corporation of Japan.

II. Related Appeals and Interferences

There are no related appeals or interferences.

III. Status of Claims

Claims 1-4, 6, 8-9, and 11-13 are pending. Claims 5, 7 and 10 are canceled. Claims 1-4, 6, and 11 are in condition for allowance. Claims 8, 9, 12, and 13 stand rejected in the Final Office Action dated February 16, 2006, and are on appeal. These claims have been at least twice rejected (see Office Actions of March 31, 2005, February 16, 2006, and the Advisory Action of June 1, 2006), and therefore are appropriately appealed at this time.

IV. Status of Amendments

All amendments to the claims have been entered.

V. Summary of Claimed Subject Matter

The claimed invention is directed to a novel lysine decarboxylase gene and the encoded protein, which has been isolated from a *Methylophilus* bacterium (see paragraphs [0015], [0022], and [0030]). The gene and the protein are the subject of claims 1-4, 6, and 11, which have been indicated as allowable. The claimed invention is further directed to a *Methylophilus* bacterium which produces L-lysine by inactivation of the novel lysine decarboxylase gene, and a method for producing L-lysine using this bacterium (see paragraph [0042] and [0067]). This subject matter is the subject of the rejected claims 8, 9, 12, and 13.

VI. Grounds of Rejection to Be Reviewed on Appeal

Whether Claims 8, 9, 12, and 13 are unpatentable under 35 U.S.C. § 103 over U.S. Patent No. 5,827,698 to Kikuchi et al. ("Kikuchi") and WO2000/61723 to Gunji et al. ("Gunji").

VIII. Argument

In the Final Rejection dated February 16, 2006, beginning at page 4, Claims 8, 9, 12, and 13 were rejected under 35 U.S.C. § 103 over U.S. Patent No. 5,827,698 to Kikuchi et al. ("Kikuchi") and WO2000/61723 to Gunji et al. ("Gunji"). For at least the following reasons, this rejection is in error and should be reversed.

A. Legal Standard

Claimed subject matter is obvious in light of the prior art if it would have been obvious to one of ordinary skill in the relevant art at the time the invention was made. 35 U.S.C. § 103(a). In considering the entire prior art in the relevant field, the claimed subject matter is obvious if the prior art "would have suggested to one of ordinary skill in the art that this [invention should be made] and would have a reasonable likelihood of success." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

Obviousness can be shown either directly by demonstrating the technical motivation to combine the prior art, *Life Technologies, Inc. v. Clontech Laboratories, Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000), or indirectly through "secondary considerations" after the claimed subject matter was invented, *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 960 (Fed. Cir. 1986). To show the motivation to combine prior art, it is not enough to simply identify different references that might be combined in hindsight; showing obviousness requires showing a motivation to combine the pieces. *Velander v. Garner*, 348 F.3d 1359, 1363 (Fed. Cir. 2003). That motivation might come from a reference or from the knowledge of an artisan of ordinary skill. The level of ordinary skill in an art is based on a number of factors, including the educational level of the inventor, the type of problems encountered in the art, prior solutions to those problems, and the speed of innovation in the art. *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 666-67 (Fed. Cir. 2000).

"Secondary considerations" focus on how the invention was received in the market; a very successful or surprising invention is probably not obvious. *See Custom Accessories, Inc.*,

807 F.2d at 960. The "secondary considerations" considered by the courts include: commercial success, copying of the invention by others, licensing of the invention, evidence of a long-felt need for the invention, skepticism by skilled artisans that the claimed invention could be achieved, prior failures of others to achieve the same result, and unexpected results. *Id.*; *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 316 (Fed. Cir. 1985). No secondary consideration is required for an invention to be non-obvious, but a court may use evidence of secondary considerations in its determination of obviousness (or non-obviousness). *Custom Accessories, Inc.*, 807 F.2d at 960.

B. The rejection of Claims 8, 9, 12, and 13 under 35 U.S.C. § 103 is in error

In the February 16, 2006 Final Office Action, claims 8, 9, 12, and 13 were rejected under 35 U.S.C. §103 over U.S. Patent No. 5,827,698 to Kikuchi et al. ("Kikuchi") and WO2000/61723 to Gunji et al. ("Gunji). Kikuchi is applied for the alleged teaching of a method for producing an increased level of L-lysine by disrupting the L-lysine decarboxylase genes (*cadA* and *ldc*) in *E. coli* using a plurality of methods including substituting a normal polynucleotide in the genome of the bacterium by a modified polynucleotide or disrupting the polynucleotides using homologous recombination. Gunji is applied for the alleged teaching of a method for producing L-lysine using a methanol assimilating bacterium, namely, *Methylophilus,* transformed with a mutant LysE and dapA genes. These genes encode aspartokinase and dihydrodipicolinate synthase, respectively, which are not subject to feedback inhibition by L-lysine. The Examiner alleges that it would have been obvious to use Kikuchi's method of disrupting the *E. coli* lysine decarboxylase gene to produce higher levels of L-lysine to disrupt a lysine decarboxylase in *Methylophilus* of Gunji.

The lysine decarboxylase gene has been isolated from *Escherichia coli,* and disruption thereof is taught in Kikuchi to increase L-lysine production by *Escherichia* bacteria. However, such a teaching does not suggest or even imply that the same gene/protein exists in *Methylophilus.* This is the invention of Appellants, and in fact, allowed claims 1-4, 6, and 11 recite the lysine decarboxylase gene/protein isolated from *Methylophilus.* The Examiner has

indicated that the discovery of a lysine decarboxylase gene from *Methylophilus* is novel and unobvious over the prior art. Appellants were able to show that the novel lysine decarboxylase gene from *Methylophilus* is only 51% homologous with the lysine decarboxylase from *E.coli* taught in the prior art.

The invention of claim 8 and 12 recite a *Methylophilus* bacterium containing the inventive DNA of allowed claim 3 and 4, and wherein the inventive lysine decarboxylase DNA is disrupted so that the lysine decarboxylase DNA is reduced or eliminated. It is unclear how a DNA sequence can be determined to be inventive, but a bacterium containing said inventive DNA in disrupted or mutated form is obvious. The Examiner has failed to explain how and why the bacterium of claims 8 and 12 is obvious over the prior art references.

Similarly, the invention of claims 9 and 13 recite a method for producing L-lysine using the bacterium of claims 8 and 12, respecively. Again, it is unclear how a method of using a bacterium containing a ***novel*** DNA sequence, wherein that ***novel*** DNA sequence is disrupted or mutated to render the encoded protein inactive, to produce L-lysine can be considered to be obvious. Again, the Examiner has failed to explain how and why the method of claims 9 and 13 is obvious over the prior art references. The reasons for these assertions are explained herein.

First, it is unclear how the Examiner can apply Gunji on such little available disclosure, particularly when this disclosure is potentially unenabling relative to the appealed claims. This reference is a WO publication in Japanese which contains a short one-sentence abstract in English. It does not appear a translation was obtained nor an English equivalent found. As pointed out on page 9 of Applicants' response filed November 14, 2005, it is unclear how the Examiner is reading and applying Gunji, since this publication contains only a short English abstract. Despite Appellant's continued requests for clarification of this point, the Examiner has merely re-applied Gunji. Interestingly, the Examiner did withdraw the US publication which was jointly cited in the First Office Action of March 31, 2005, which the Examiner incorrectly believed to be an equivalent to Gunji. As Gunji is assigned to the same company as the instant application, Applicants have provided their description of the teachings. However, it is still unclear how the Examiner can apply Gunji when he has not addressed whether he can

understand the reference, nor does he point to the specific teachings in the reference on which he is relying, nor does he state that he is relying on Applicant's characterization. It is asserted that no *prima facie* case of obviousness can be made when support in the relied upon reference is not pointed to or clarified.

Secondly, Appellants assert that Kikuchi et al. would not lead one of ordinary skill in the art to determine the gene sequence of the novel lysine decarboxylase from *Methylophilus* (now allowable in the form of claims 1-4 and 6). There is no indication in the prior art that such a gene even exists in *Methylophilus* bacterium. Certainly, if it is not obvious to one of ordinary skill in the art to determine the gene sequence of the claimed lysine decarboxylase from *Methylophilus*, then it is unclear how one of ordinary skill in the art would be able to isolate a bacterium containing the inventive lysine decarboxylase from *Methylophilus* ***in disrupted form***, and determine a method of making L-lysine using said bacterium. There is no teaching in either reference that a lysine decarboxylase gene even exists in *Methylophilus.* Appellants were the first to isolate such a gene, and as it turns out, the novel gene from *Methylophilus* is only 51% homologous to the known gene taught by Kikuchi. Even if, *arguendo,* one of skill in the art knew the percent homology between the lysine decarboxylase genes from *E. coli* and *Methylophilus*, it does not appear one of skill in the art would be motivated to disrupt the gene from *Methylophilus* for the purpose of increase production of L-lysine since the proteins are so different in their structure, and their functions in their respective native bacterial species are largely unknown. Hence there is no motivation to combine these references.

Therefore, a reading of the reference of Kikuchi would not motivate the person of skill in the art to isolate the novel lysine decarboxylase from *Methylophilus*, as has already been determined by the indication of allowance of claims 1-2, 6, and 11. Furthermore, Kikuchi fails to motivate with any expectation of success the skilled art worker to disrupt a lysine decarboxylase gene in *Methylophilus* since at the time of the invention, it was not even know that such a gene even exists, nor what its simlarity it possessed to the know lysine decarboxylase gene/protein from *E. coli.*

Gunji fails to make up for the above-noted deficiencies of Kikuchi. Although Gunji

teaches that *Methylophilus* is capable of producing L-lysine, there is no indication in Gunji that a lysine decarboxylase gene such as that taught in Kikuchi, is even present in *Methylophilus.* This fact alone does not provide the necessary motivation to combine the teachings of these two references. Furthermore, one of skill in the art would additionally not be motivated to combine the teachings of these references since there is no indication that a homolog of the gene of Kikuchi, which Appellants have shown is very dissimilar as compared to the claimed (and allowed) gene, if present in *Methylophilus,* would function in the *Methylophilus* the same way that the lysine decarboxylase gene function in *Escherichia,* and especially that when disrupted, that the result in *Methylophilus* would be simliar to the effect of a similar disruption in *Escherichia.* Therefore, one of skill in the art would not be able to determine from the combination of these references that 1) a homolog of lysine decarboxylase exists in *Methylophilus,* and if so 2) that such a homolog would function in the same way in *Methylophilus* as its homolog does in *Escherichia,* and finally, 3) that when disrupted, a simliar effect would be seen in *Methylophilus* as is seen in *Escherichia* vis a vis production of L-lysine.

More specifically, Kikuchi et al. describe a lysine decarboxylase gene which is only 51% homologous with the novel nucleotide sequence of SEQ ID NO:3. The sequences are very dissimilar and hence one of ordinary skill in the art would not be expected to arrive at the inventive DNA sequence, the *Methylophilus* bacterium, and/or the disrupted gene resulting in suppression of lysine decarboxylase activity, without undue experimentation. As claims 8 and 12 recite that the DNA of claims 3 and 4, respectively, is disrupted, clearly the skilled art worker would not have motivation to arrive at the DNA sequence, disrupt it, and use it in a *Methylophilus* bacterium to produce L-lysine, even in light of the teaching that *Methylophilus* is capable of producing L-lysine. Deducing the DNA of claims 3 and 4 from the disclosure of Kikuchi is clearly not expected, and in fact, there is clearly no motivation to arrive at the inventive DNA of claims 3 and 4 based upon the dissimilar DNA sequences, and therefore, there is no motivation for arriving at the bacterium or method of claims 8 and 12.

Again, Gunji fails to make up for the deficiencies of Kikuchi with respect to the subject matters of the pending claims, since Gunji only describes the use of *Methylophilus* bacteria for

producing L-amino acids, and discloses nothing of disrupting any gene for any purpose, and certainly not for the purpose of suppressing lysine decarboxylase activity. Furthermore, Gunji et al. does not mention the lysine decarboxylase gene of any sequence. Since there is no mention of a lysine decarboxylase gene, there is certainly no motivation to combine this disclosure with the disclosure of Kikuchi, which only teaches a lysine decarboxylase which is only 51% homologous to the novel lysine decarboxylase of the present invention.

For at least the foregoing reasons, Applicant respectfully submits that the subject matters of Claims 8, 9, 12, and 13, each taken as a whole, would not have been obvious to one of ordinary skill in the art at the time of Applicant's invention, are therefore not unpatentable under 35 U.S.C. § 103(a), and therefore respectfully requests withdrawal of the rejection thereof under 35 U.S.C. § 103(a).

IX. Conclusion

For at least the foregoing reasons, Appellants respectfully submit that the subject matters of Claims 8, 9, 12, and 13, each taken as a whole, are patentable. Accordingly, Appellants respectfully request reversal of the rejections of Claims 8, 9, 12, and 13 under 35 U.S.C. §103.

Respectfully submitted,

By: _____

Shelly Guest Cermak
Registration No. 39,571

U.S. P.T.O. Customer Number 38108
Cermak & Kenealy, LLP
515-B E. Braddock Road
Alexandria, VA 22314
703.778.6608 (v)
703.652.5101 (f)

Date: January 17, 2007

APPENDIX A: CLAIMS ON APPEAL

1. An isolated protein selected from the group consisting of:

(A) a protein which has the amino acid sequence of SEQ ID NO: 4; and

(B) a protein which has the amino acid sequence of SEQ ID NO: 4 including substitution, deletion, insertion or addition of one to 20 amino acid residues and has lysine decarboxylase activity.

2. An isolated protein selected from the group consisting of:

(A) a protein which has the amino acid sequence of SEQ ID NO: 4; and

(B) a protein which has the amino acid sequence of SEQ ID NO:4 including substitution, deletion, insertion or addition of one to 10 amino acid residues and has lysine decarboxylase activity.

3. An isolated DNA encoding a protein selected from the group consisting of:

(A) a protein which has the amino acid sequence of SEQ ID NO: 4; and

(B) a protein which has the amino acid sequence of SEQ ID NO: 4 including substitution, deletion, insertion or addition of one to 20 amino acid residues and has lysine decarboxylase activity.

4. An isolated DNA encoding a protein selected from the group consisting of:

(A) a protein which has the amino acid sequence of SEQ ID NO: 4; and

(B) a protein which has the amino acid sequence of SEQ ID NO: 4 including substitution, deletion, insertion or addition of one to 10 amino acid residues and has lysine decarboxylase activity.

6. The DNA of claim 3, which is isolated from the genome of a *Methylophilus* bacterium.

8. A *Methylophilus* bacterium which produces L-lysine, wherein a polynucleotide on the

genome is disrupted, wherein said polynucleotide is the DNA of claim 3, and thereby the intracellular lysine decarboxylase activity is reduced or eliminated.

9. A method for producing L-lysine, comprising the steps of culturing the *Methylophilus* bacterium of claim 8 in a medium containing methanol as a major carbon source resulting in accumulation of L-lysine in culture, and collecting the L-lysine from the culture.

11. The DNA of claim 4, which is isolated from the genome of a *Methylophilus* bacterium.

12. A *Methylophilus* bacterium which produces L-lysine, wherein a polynucleotide on the genome is disrupted, wherein said polynucleotide is the DNA of claim 4, and thereby the intracellular lysine decarboxylase activity is reduced or eliminated.

13. A method for producing L-lysine, comprising the steps of culturing the *Methylophilus* bacterium of claim 12 in a medium containing methanol as a major carbon source resulting in accumulation of L-lysine in culture, and collecting the L-lysine from the culture.

APPENDIX B: EVIDENCE

None.

APPENDIX C: RELATED PROCEEDINGS

None.